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Clinical Trials of Intracoronary Bone Marrow Cell Transfer after Myocardial Infarction: The Hannover Experience

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Autologous bone marrow cells • Acute myocardial infarction • Ejection fraction

Experimental studies suggesting that cardiac transfer of unfractionated bone marrow cells (BMCs) or bone marrow–derived stem and progenitor cells enhances functional recovery after myocardial infarction have caused much excitement [1-4]. On the basis of these studies and the more general concept of adult stem cell plasticity, it has been proposed that bone marrow–derived stem and progenitor cells may be used for cardiac tissue repair in patients after acute myocardial infarction [1,5]. Early clinical investigations indicate that infusion of autologous BMCs into the infarct-related coronary artery is feasible after acute myocardial infarction [6,7]. However, because of the nonrandomized design of these studies, the efficacy of intracoronary BMC transfer for functional recovery after myocardial infarction in patients has remained uncertain. We conducted a prospective, randomized, controlled trial to determine the effect of intracoronary autologous BMC transfer on left ventricular functional recovery in patients after acute myocardial infarction and successful percutaneous coronary intervention (PCI) [8]. After successful PCI for acute ST segment elevation myocardial infarction, we randomized patients to a control group (30 patients) that received optimal postinfarction medical therapy and a BMC transfer group (30 patients) that received optimal medical therapy and intracoronary transfer of autologous BMCs 5 days after PCI. The left ventricular ejection fraction (LVEF) change from baseline to 6-month follow-up, as determined by cardiac magnetic resonance imaging, was the prespecified primary end point of the trial. After 6 months, the LVEF had increased by 0.7 percentage points in the control group and 6.7 percentage points in the BMC transfer group ($P = .0026$). BMC transfer enhanced left ventricular systolic function primarily in the infarct border zone. The improvement in global LVEF at 6-month follow-up was not correlated with the number of nucleated cells, $CD34^+$ cells, or hematopoietic colony-forming cells infused into the infarct-related coronary artery. BMC transfer did not increase the risk of adverse clinical events, including in-stent re-stenosis or proarrhythmic effects. We now have also used labeling of BMCs and positron emission tomography scanning to monitor the homing of these cells into the myocardium after infarction in a subset of patients and identified labeled cells within the infarcted myocardium. These studies suggest that only a fraction of cells infused into the coronary circulation are homing in the heart. It is interesting to note that the percentage of homing cells can be enhanced by selection of bone marrow–derived $CD34^+$ cells, and the latter approach is associated with preferential homing into the infarct border zone. We are currently performing prolonged follow-up studies of our patients to establish the long-term safety and efficacy of this therapeutic intervention (Figure 1).

Our studies suggest that intracoronary transfer of autologous BMCs seems safe and promotes improvement of left ventricular systolic function in patients after acute myocardial infarction. However, large double-blind randomized trials are required to show a beneficial effect not only on ejection fraction, but also on clinical end points and, ultimately, on survival. Such studies involving 200 patients are

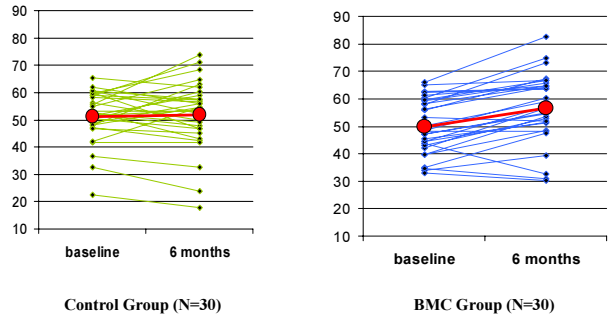

Figure 1. Left ventricular ejection fraction as determined by magnetic resonance imaging. BMCs were infused via the central lumen of an over-the-wire balloon catheter. To maximize the contact time of BMCs with the inner surface of the infarct-related microcirculation, the balloon was inflated inside the stent to transiently interrupt antegrade blood flow during infusions. An average of $9 \pm 6 \times 10^6$ $CD34^+$ cells were infused into the infarct-related coronary artery the same day as bone marrow harvesting.

now under way or are about to start. In the meanwhile, experimental studies are mandatory to elucidate the underlying mechanisms, which most likely are not confined to the differentiation of these cells into cardiomyocytes [9,10] but rather expand to the paracrine effects of the cells applied [11,12].

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